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Controversies in the use of nutritional supplements in ophthalmology

John G Lawrenson[1] and Andrzej Grzybowski[2]

1. *Centre for Public Health Research, School of Health Sciences, City University London, London UK*
2. *University of Warmia and Mazury, Olsztyn, Poland*

Corresponding author:

Professor JG Lawrenson

Centre for Public Health Research,

School of Health Sciences, City University London,

London UK

EC1V 0HB

Tel: +44 2070404310

Email: j.g.lawrenson@city.ac.uk

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Abstract

Nutritional supplements are widely taken by the general population and several of these products are marketed specifically to improve eye health. The aim of this review is to summarise the evidence for the benefit of supplementation with antioxidant vitamins and other micronutrients for three of the most common eye diseases of the elderly: age-related macular degeneration (AMD), cataract and dry eye syndrome (DES). Although the potential importance of diet and nutrition in these conditions is strongly supported by data from observational studies, evidence from randomised controlled trials (RCTs) on the benefit of nutritional supplementation is generally lacking. However, there is high quality evidence to support the use of an Age-Related Eye-Disease Study (AREDS) supplement containing antioxidants (β-carotene, vitamin C and vitamin E) and zinc to slow progression in those at moderate to high risk of developing advanced AMD. Recent data from the AREDS2 trial provided data to suggest that β-carotene could be replaced with lutein and zeaxanthin on the based on improved safety without compromising efficacy. Although there is currently insufficient evidence to recommend the routine use of any of the commercially available supplements in cataract and DES, given the public health importance of these conditions further research into the benefit of dietary modification or nutritional supplementation should be a priority.

Introduction

Based on data from large cross-sectional surveys, it has been estimated that up to two thirds of the adult population of the US regularly takes one or more nutritional supplements [1, 2]. These are most often combinations of vitamins and minerals, but products containing essential fatty acids (EFA) or other micronutrients are also commonly used. Nutritional supplement use tends to be more common among women than men and the likelihood of taking supplements generally increases with age [3]. The most frequently reported motivation for taking these products is to maintain or improve overall health and supplement users tend to be better educated and more likely to adopt healthy lifestyle behaviours than non-users [4]. Despite their widespread use, high quality evidence that vitamin and mineral supplements improve general health outcomes or prolong life is lacking and it is possible that high doses of certain micronutrients may be harmful [5]. Systematic reviews of randomised controlled trials (RCT) for primary prevention have shown that antioxidant supplements do not seem to prevent cancer, cardiovascular diseases, or death [6, 7]. A meta-analysis combined with trial sequential analysis of 53 trials with a low risk of bias found that supplements containing beta-carotene and vitamin E in doses higher than the recommended daily allowance (RDA) were associated with a significant increase in mortality [8]. It is important to note that most placebo controlled trials of supplements for primary and secondary prevention are conducted in industrialised countries in generally well-nourished populations. It is therefore not possible to rule out a benefit of supplementation in nutritionally compromised individuals. However, for the general population current evidence suggests that the case for vitamin supplementation to improve health outcomes is poor. In 2013, an Editorial in Annals of Internal Medicine [9] concluded:

'Although available evidence does not rule out small benefits or harms or large benefits or harms in a small subgroup of the population, we believe that the case is closed- supplementing the diet of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful. These vitamins should not be used for chronic disease prevention. Enough is enough.'

The potential value of specific combinations of micronutrients to improve eye health is frequently promoted by micronutrient manufacturers as 'eye nutrients' and approximately 4% of supplement usage is reported to be specifically for this purpose [4]. The well-publicised results of large National Eye Institute (NEI)-funded trials in the US (Age-Related Eye Disease Study (AREDS) and AREDS2), demonstrating the value of antioxidant supplements in reducing the risk of developing advanced age-related macular degeneration (AMD), may have further contributed to their widespread use and promotion in the elderly. Recent surveys of optometrists and ophthalmologists have revealed that nutritional supplementation is now part of routine clinical practice for patients with or at risk of AMD [10, 11] although these recommendations are frequently not evidence-based [10]. The aim of this mini-review is to consider evidence for the value of nutritional supplementation in three

common age-related eye diseases: AMD, cataract and dry eye. The article will summarise data from recently published systematic reviews on nutritional supplementation published by the Cochrane Eyes and Vision Group.

Age-related macular degeneration

Although in global terms, AMD ranks third as the leading causes of visual impairment [12], it is the most common cause of blindness in European-derived populations. For example in the UK, AMD is responsible for over 50% of blind and partially sighted registrations [13] and with an ageing population the prevalence of the disease is predicted to increase substantially [14]. In addition to the obvious personal impact of AMD, the societal burden is also considerable. Economic costs arise from both the direct costs of treatment as well as indirect costs associated with visual impairment, including the provision of social care [15]. Although treatments in the form of anti-vascular endothelial growth factor inhibitors are available that can slow the progression of the neovascular form of the disease (so called 'wet' AMD), there is still no effective treatment for atrophic ('dry') AMD, which affects over 90% of sufferers. It is likely that the pathogenesis of AMD is multi-factorial, arising from the complex interplay between genetic and environmental factors [16]. Oxidative stress has been implicated as a causative factor in the development of AMD, since the action of light on retinal photoreceptors generates potentially damaging free radicals [17]. Although the presence of macular pigment is thought to limit cellular damage by absorbing incoming blue light and/or quenching free radicals, it has been proposed that AMD could occur due to the cumulative effects of oxidative damage on macular photoreceptors and the underlying retinal pigment epithelium (RPE) [17]. Consequently, increased consumption of antioxidants through the diet has attracted significant interest as a simple, widely applicable and cost-effective intervention. Observational studies have reported that dietary components such as antioxidant vitamins and certain carotenoids can reduce the risk of developing AMD or slow its progression (see [18] for a recent review). However, results from these non-experimental studies should be interpreted with caution, since people with a diet rich in particular nutrients may differ in other ways from those who do not. The highest quality evidence to assess the benefit of nutritional supplementation comes from randomised controlled trials (RCTs), where participants have been randomly allocated to receive either a dietary supplement or a placebo/no intervention. Evidence arising from such trials has been reviewed in two related Cochrane Systematic Reviews that were published in 2012 [19, 20] and a recently updated review in 2015 [21]. Two of these reviews focussed on the role of antioxidant vitamin and mineral supplements in the prevention [19] and progression [20] of AMD and one review investigated on the role of omega-3 fatty acid supplementation [21].

The review on 'antioxidant vitamin and mineral supplements for preventing age-related macular degeneration' [19] included data from 4 trials, which provided high quality evidence that people aged 40 years and above in the general population are unlikely to prevent the development of AMD by taking supplements containing vitamin E (data from 3 trials) or β-carotene (provitamin A) (2 trials). The included RCTs were large (enrolling between 1000 and 40 000 participants), conducted so as to avoid bias, and were consistent with each other. The pooled risk ratio (RR) for any antioxidant supplement in the prevention of any AMD was 0.98 (95% confidence interval 0.89 to 1.08) and for advanced AMD was 1.05 (95% CI 0.80 to 1.39). The review was unable to identify RCTs with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations.

The Cochrane review "Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration" [20] included data from 13 trials, although these were generally small. Over half the participants were randomised in one trial (AREDS), which found a beneficial effect of antioxidant (β-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio (OR) 0.68, 95% CI 0.53 to 0.87) over an average of 6.3 years (Figure 1).

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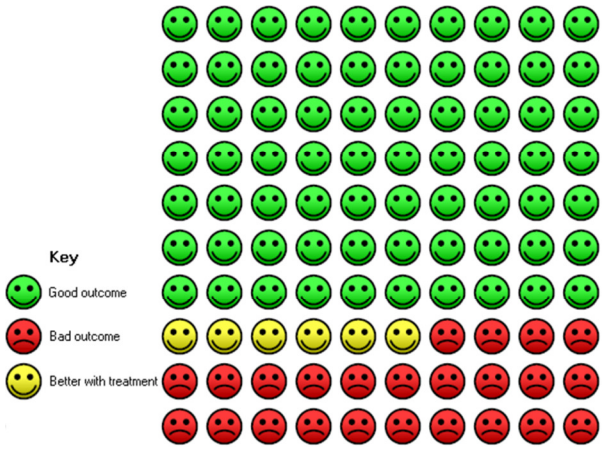

Figure 1. *Cates plot illustrating the effect of antioxidant and mineral supplements in slowing the progression of AMD (data taken from [20]). In the control group approximately 30 people in 100 had progressed to advanced AMD over 6.3 years, compared to 24 (95% CI 20 to 28) out of 100 for the supplemented group.*

People taking supplements were also less likely to lose 15 or more letters of visual acuity on a standard EDTRS chart (adjusted OR 0.77, 95% CI 0.62 to 0.96). The other 12 trials included in the review were generally small with shorter follow-up periods (less than two years). No evidence for an effect of supplementation was seen in these smaller trials of shorter duration. Since this review was written, the results of the AREDS2 trial have been published [22]. The rationale for this new study was the observational data that suggested that a high dietary intake of omega-3 fatty acids or increased consumption of the xanthophyll's lutein and zeaxanthin were associated with a decreased risk of developing AMD [23]. Lutein and zeaxanthin are major constituents of the macular pigment and possess antioxidant and *UV* light filtering properties and so protect the photoreceptors and RPE from damage [24].

In AREDS2 participants took the original AREDS formulation (or a variation of thereof) as 'standard care' and were randomly assigned, using a factorial design, to additionally receive a placebo or a capsule containing lutein/zeaxanthin and/or omega-3 long chain polyunsaturated fatty acids (LCPUFA) . Patients were followed up for a median period of 5 years. The primary analysis found that the addition of lutein and zeaxanthin to the original supplement did not confer any additional benefit regarding progression to advanced AMD (hazard ratio (HR) 0.90, 98.7% CI 0.76 to 1.07) [22]. However, further exploratory analyses of the trial data, which compared those taking and not taking lutein/zeaxanthin suggested that lutein and zeaxanthin may be a more appropriate component of the AREDS formula than the β-carotene in the original formula [25]. The secondary analyses of a direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.82 (95% CI, 0.69-0.96; p = 0.02) for development of any late AMD, 0.78 (95% CI, 0.64-0.94; p = 0.01) for the development of neovascular AMD, and 0.94 (95% CI, 0.70-1.26; p = 0.67) for development of central geographic atrophy. Eliminating β-carotene could also be argued to be beneficial on safety grounds. The Alpha Tocopherol-Beta-Carotene Cancer Prevention (ATBC) Study, which investigated the impact of supplemental α-tocopherol and β-carotene on cancer incidence in male smokers, found that β-carotene increased lung cancer incidence by 17% and overall mortality by 8%. [26]. Although the switch of carotenoids in the AREDS formula seems reasonable, it should be pointed that as with β -carotene 15 years ago, the long-term safety profile of this combination is unknown. Moreover, if lutein and zeaxanthin are the optimal carotenoids to be used, further work is required to determine the most effective dose [27].

AMD is a complex disease in which individual susceptibility is determined by a combination of genetic and environmental risk factors. There has been a significant interest in whether the beneficial effect of nutritional supplements is influenced by particular AMD genotypes [28-30]. Klein and co-workers provided some evidence for a treatment interaction in those AREDS participants with the complement factor H (CFH) genotype [28], which was specifically related to the zinc component of the formulation. A subsequent analysis of AREDS data similarly found that the response to supplementation was linked to specific genetic polymorphisms [29] and the study authors made the case for genotype-directed nutritional therapy. However, these findings could not be

confirmed in a recent retrospective analysis of a larger cohort of AREDS participants [30]. This study also highlighted serious methodological flaws in the sub-group analysis used in the previous study [29] and concluded that the AREDS supplement reduced the rate of progression of AMD across all genotype groups.

There is a plausible biological rationale for supplementing with dietary omega-3 fats to prevent or slow the progression of AMD. The omega-3 fatty acid docosahexaenoic acid (DHA) accounts for 50% to 60% of the total fatty acid content of the outer segments of photoreceptors [31]. The constant turnover of outer segment membranes requires a continuous dietary supply of DHA or its precursors and a deficiency may therefore predispose to the development of AMD [31]. Further evidence comes from observational studies, which have reported that the consumption of fish or foods rich in omega-3 long-chain polyunsaturated fatty acids (LCPUFA) could reduce the risk of developing AMD [32-36]. Similarly, a nested cohort study within the Age-Related Eye Disease Study (AREDS) found that participants at moderate to high risk of progressing to late AMD, who reported the highest consumption of omega-3 LCPUFA, were 30% less likely to develop advanced AMD when compared to those reporting the lowest consumption [37]. The recently updated Cochrane review 'Omega-3 fatty acids for preventing or slowing the progression of age-related macular degeneration' [21] included two relevant RCTs [22, 38]. In one of the treatment arms of AREDS2 [22], subjects aged 50-85, at high risk of progressing to advanced AMD, were randomised to receive a daily dose of the omega-3 LCPUFA, DHA and eicosapentaenoic acid (EPA) or a control supplement. The median follow up period was 5 years. In the Nutritional AMD Treatment 2 (NAT-2) study [38], people aged 55-85 with neovascular AMD in one eye and intermediate AMD in the other were randomly assigned to receive a daily supplement containing DHA and EPA or a placebo for a period of 3 years. In both trials, the main outcome measures were the development of advanced AMD and progression to moderate or worse vision loss (defined as a loss of 15 or more letters on a standard EDTRS letter chart). The trials, which had a low risk of bias, provided high quality evidence that people taking omega-3 LCPUFA supplements were not at a decreased (or increased) risk of developing advanced AMD. The pooled HR for progression of AMD was 0.96, 95% CI 0.84 to 1.10 [21].

In summary, the lack of an effective treatment for the majority of individuals with AMD represents a major public health problem. Most of the available evidence on diet and nutrition comes from cohort studies,where residual confounding from other lifestyle variables is always a problem. Such confounding can be avoided in RCTs, although such trials are expensive to conduct and are generally of short duration. The results of the landmark AREDS trial provided high quality evidence that people with AMD may experience a modest delay in progression of the disease by supplementation with a specific combination of antioxidants (vitamins C, E and β-carotene) and zinc. AREDS2 concluded that lutein/zeaxanthin may be a more appropriate than β-carotene in AREDS-type supplements, given the valid safety concerns regarding this component. There are a number of unanswered questions; patients recruited into these trials were well nourished with an above average intake of dietary nutrients and it is not clear whether the results can be applied to the population as a whole. There is also limited data on the long-term safety of these supplements. In terms of primary prevention, there is currently no evidence that commonly marketed micronutrient formulations prevent the development of AMD.

Cataract

Cataract is defined as any visible opacity within the substance of the ocular lens and is further classified on the basis of its anatomical location: cortical, nuclear or posterior sub-capsular [39]. Oxidative stress has been implicated in the pathogenesis of all cataract sub-types [39]. With advancing age, lens proteins become increasingly susceptibility to oxidative damage and post-translation modification leading to impaired visual acuity and a reduction in contrast sensitivity [39]. Age-related cataracts are the leading cause of blindness worldwide and are responsible for 51% of blindness in the population over 50, corresponding to approximately 20 million people [12]. Supplementation with dietary antioxidants has been proposed as a strategy for cataract prevention and several observational studies have found an association between consumption of antioxidant vitamins or particular carotenoids and a reduced risk of cataract development (see [40] for a recent review). However, not all of these data are consistent and there is a risk that the reported outcomes may be subject to bias

and confounding. A Cochrane Systematic Review 'Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract' was published in 2012 [41] and included data from 9 trials of generally high methodological quality, in which 117,272 individuals over the age of 35 had been randomised to receive antioxidant vitamins (β-carotene, vitamin C and vitamin E, used alone or in combination) or placebo. In the pooled analysis, there was no evidence of effect for β-carotene in reducing risk of cataract (2 trials) (RR 0.99, 95% CI 0.91 to 1.08) or reducing rates of cataract extraction (3 trials) (RR 1.00 95% CI 0.91 to 1.10), vitamin E in reducing risk of cataract (3 trials) (RR 0.97, 95% CI 0.9 to 1.04) or cataract extraction (5 trials) (RR 0.98 95% CI 0.91to 1.04). Similarly, data from one RCT comparing vitamin C to placebo found no difference in rate of incident cataract (HR 0.97, 95% CI 0.85 to 1.12). The review authors concluded that 'costs and adverse effects [*of taking antioxidants to prevent cataracts]* should be weighed carefully with unproven benefits before recommending their use'.

Cataract outcomes were also included in the AREDS and AREDS2 trials. The original AREDS study reported that the use of a supplement containing antioxidant vitamins (β-carotene, vitamin C, vitamin E) and zinc did not affect the development or progression of lens opacities over the trial period [42]. Similarly, AREDS2 found that the addition of lutein/zeaxanthin to the original AREDS formulation had no effect on the rates of cataract surgery or moderate vision loss [43].

In summary, despite encouraging results from observational studies, RCTs that have evaluated the effect of particular antioxidant vitamins and carotenoids on the development of cataract or cataract extraction have failed to consistently establish a causal association or benefit. The lack of an effect of antioxidants in these relatively short-term trials could suggest that longer-term intake is required or that formulations containing multiple antioxidants are necessary to provide a clinically significant benefit. Using the AREDS cohort and a Cox regression analysis of baseline factors that predicted cataract, the use of multivitamin supplements (Centrum, Wyeth Consumer Healthcare) was found to be associated with a lower risk of developing nuclear cataracts over an average of 9.8±2.4 years follow up [44]. This finding was consistent with the results of a RCT conducted in Italy [45] that was not included in the Cochrane review, although intriguingly in this study multivitamin use was associated with an increased risk of posterior sub-capsular cataracts. Cataract outcomes based on participant reports were also investigated in the multivitamin arm of the Physicians' Health Study II (PHS II), a large-scale randomised trial of middle-aged and older men [46]. This study found that long-term daily multivitamin use was associated with a 9% lower risk of cataract compared to placebo (HR, 0.91; 95% CI, 0.83–0.99; p=0.04). Given the high prevalence of cataract in the elderly population [47], even a modest reduction in risk of cataract would potentially have a large public health impact, however potential benefits need to be balanced against the risk of harm.

Dry Eye Syndrome

Dry eye syndrome (DES) is one of the most common ophthalmic conditions in the world with an estimated prevalence of 5-30% of the population aged 50 and above [48]. DES occurs where the eye does not produce enough tears or where the tears evaporate too quickly. The condition is associated with inflammation of the ocular surface and leads to reduced ocular comfort, varying degrees of visual disturbance and a corresponding reduction in quality of life [49]. There has recently been a great deal of interest in the potential for oral supplementation with essential fatty acids (EFAs), specifically omega-3 and omega-6 LCPUFA, as an adjunct to conventional treatments in DES. Increased consumption of omega-3 fatty acids has been advocated in evidence-based reviews and professional guidance on DES and associated conditions such as meibomian gland dysfunction [50-52]. Omega-3 and omega-6 EFA, which must be obtained from the diet, are precursors of eicosanoids that are locally-acting signalling molecules which regulate inflammation. Omega-3 LCPUFAs such as DHA and EPA are present in certain vegetable oils (e.g. flaxseed oil) and in oils from cold water fish and other marine animals. Omega-6 fatty LCPUFA e.g. arachidonic acid and linoleic acid are found in sunflower oils, evening primrose oil and animal fats. Omega-6 fatty acids e.g. linoleic (LA) can be metabolised into the pro-inflammatory mediators prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) via the arachidonic acid pathway or into less potent inflammatory mediators e.g. prostaglandin E1 (PGE1). Similarly, omega-3 LCPUFA

e.g. EPA, which act competitively for the enzymes cyclooxygenase and lipoxygenase, are metabolised into the less biologically active 3-series prostaglandins (Figure 2). The balance between intake of omega-3 and omega-6 LCPUFA is likely to be a key factor in modulating the bodies' inflammatory response and it can therefore be hypothesised that optimising the omega-3/omega-6 ratio may mitigate against the signs and symptoms associated with DES.

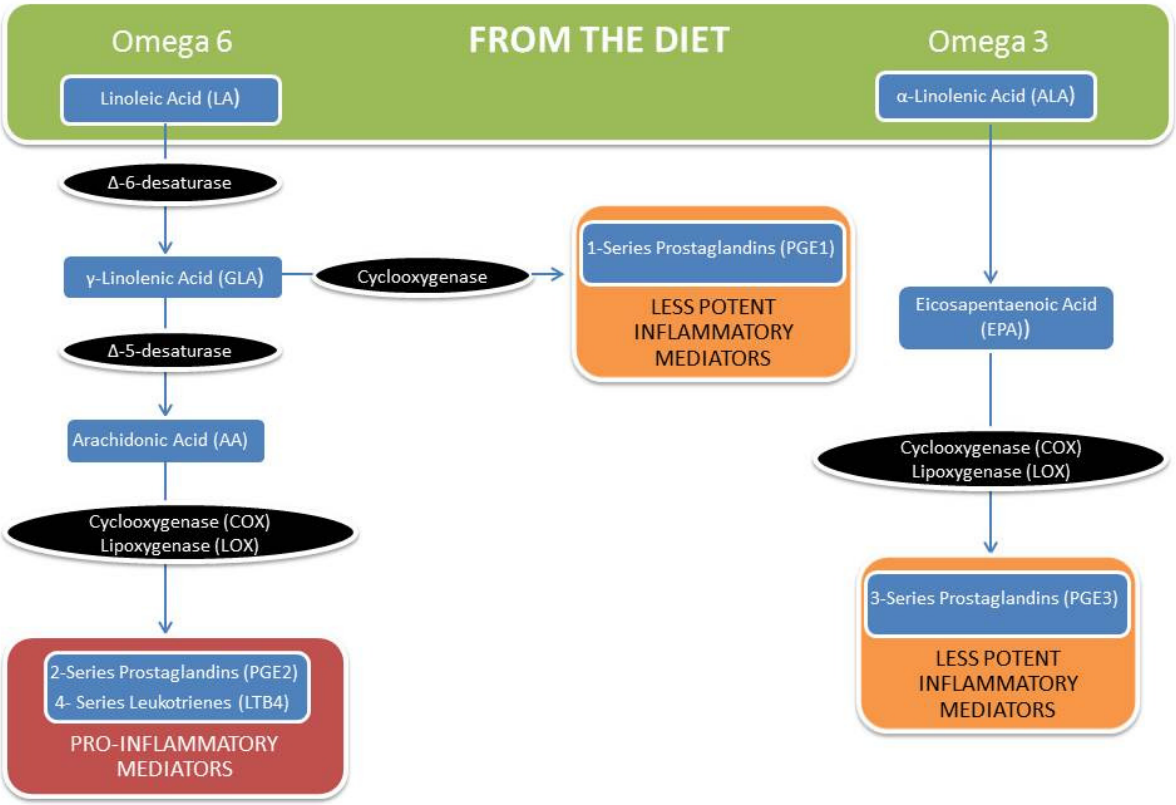

Figure 2. *Metabolic pathways for dietary omega-3 and omega-6 EFA in eicosanoid synthesis.*

There is compelling data from observational studies on the value of increasing dietary intakes of omega-3 fats. For example, in a subset of participants in the Women's Eye Study in the US (N=32,470) a higher intake of omega-3 was inversely associated with the incidence of DES [53]. By contrast, data from intervention studies on the benefit of supplementation with EFA are sparse. A recent systematic review [54] of RCTs investigating omega-3 LCPUFA for DES included data from 7 trials involving 720 participants. Although pooled data found a small but statistically significant increase in tear stability and quality, it is debatable whether these differences would be clinically meaningful. Importantly no difference was found in the Ocular Surface Disease Index (which assessed the severity of symptoms associated with dry eye). In summary, although there is some evidence for the effectiveness of EFA supplementation in DES, more data is needed before supplements can be widely recommended.

Conclusions

A large percentage of the general population is taking a diverse range of nutritional supplements to maintain or improve their overall health without any evidence-based justification. Supplementing the diet of well-nourished adults with mineral or vitamin supplements appear to have no clear benefit and might even be harmful. It is important that any advice given regarding supplements is informed by the best available research evidence. However, there is a dearth of high quality data from randomised trials on the effectiveness of these preparations for common age-related eye conditions such as AMD, cataract and DES. It should also be borne in mind that the use of high dose micronutrient supplements also has the potential for harm, for example several trials have reported higher rates of lung cancer in cigarette smokers who were taking nutritional supplements containing β-carotene and there is also the possibility of interactions of nutritional supplements with prescribed medications [55]. Currently there is insufficient evidence to recommend commercially available supplements for the prevention or treatment of cataract or DES. However, there is high quality evidence to support the use of an AREDS-formulation supplement containing antioxidants (β-carotene, vitamin C and vitamin E) and zinc to slow progression in those patients at high risk of developing advanced AMD, including those with intermediate AMD in one or both eyes (AREDS category 3) or advanced AMD (AREDS category 4) in one eye, but not the other eye. Recent data from the AREDS2 trial provided further evidence that β-carotene in the original AREDS formula could be replaced with lutein and zeaxanthin on the basis of improved safety without compromising efficacy. Given the current scale of the public health problem caused by age-related eye disease and with increasing longevity, reducing the risk of developing these diseases or slowing their progression through dietary modification should remain an important area for future research.

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